

Ups and downs—and ups in the antiviral therapy of HIV infection

I V D Weller, I Williams

In the first randomised placebo controlled trial of zidovudine in symptomatic HIV disease in 282 patients who had AIDS or AIDS related complex a survival benefit was demonstrated.¹ The trial was interrupted with an average follow-up of only around four months. One death had occurred in the treatment group, 19 in the placebo and there was a reduction in the probability of developing an opportunistic infection. This trial led to the licensing of zidovudine for symptomatic disease in 1987. Until very recently it was the only study of antiviral therapy to have shown an effect on mortality. At the same time trials were established to determine whether use of the drug earlier in infection was beneficial.

In 1989 two studies showed that zidovudine may delay progression to severe ARC and AIDS in patients with early symptomatic disease and in those that were symptomless with CD4 counts $< 500/\mu\text{l}$.^{2,3} The average follow-up of both trials was around one year. The trial in symptom-free patients (AIDS Clinical Trials Group (ACTG) protocol 019), was interrupted in those patients with CD4 counts $< 500/\mu\text{l}$ because of a significant delay in disease progression. There were a total of 74 AIDS and ARC events amongst 1338 patients randomised to placebo, low dose zidovudine (500 mg daily) or high dose zidovudine (1500 mg daily). There were 38, 17 and 19 events in the placebo, low dose and high dose arms respectively. Because of a 6.3% incidence of severe haematological toxicity with the high dose compared to 1.1% with the low dose, 500 mg of zidovudine was recommended for the treatment of symptom-free patients with CD4 counts $< 500/\mu\text{l}$.

In 1992 a study was completed in 1013 patients who had been on zidovudine for an average of two years and randomised to either continue zidovudine or switch to didanosine (ddI).⁴ There were two didanosine arms, a low dose (500 mg daily) and a higher dose (750 mg daily). There was a significant delay in the progression time to a new AIDS diagnosis in the low dose group compared to the zidovudine group but no detectable effect on mortality. There were over 300 patients in each arm and there were 125 events in zidovudine arm and 115 and 94 in the high and low dose groups respectively. The relative risk of progression to a primary endpoint in the zidovudine group compared to the low dose ddI group was 1.39 (95% confidence limits 1.06–1.82 ($p = 0.015$)). As a result of these studies, many hoped that zidovudine in the mid to long term would continue to benefit

those with symptomless infection. Furthermore, it appeared that at some stage switching to didanosine in zidovudine exposed patients was better than continuing zidovudine in terms of delaying disease progression. Hopes were raised that the transient modest rises in CD4 cells and decrease in virus levels induced by therapy would be shown to capture an important mid to long term clinical benefit and that at some stage controlled trials in HIV infection might be shortened by using surrogate rather than clinical endpoints. We were on an “up”.

Then came the “downs”. In 1992 a study which compared immediate versus deferred zidovudine therapy in patients with early symptomatic disease and CD4 counts between 200 and $500/\mu\text{l}$ showed that there was no significant difference between the two groups in survival or progression to AIDS or death after a mean follow-up of more than two years.⁵ Progression to AIDS was reported to have been delayed in the immediate group when all deaths before AIDS were censored, an analysis that assumes that such deaths are neither HIV or drug related.

In 1993 the first results of the Concorde study were announced.⁶ This study in symptomless patients over three years detected no important clinical benefit when immediate and deferred treatment policies were compared that is, starting zidovudine immediately (after randomisation) or delaying it until the onset of symptomatic disease or at a CD4 count at which such an onset was imminent. There were 176 and 171 AIDS or death events in the immediate and deferred arms respectively. Following the Concorde study three European and Australian trials were published comparing zidovudine with placebo in symptomless infection.⁷⁻⁹ Two studies had too few endpoints to draw any firm conclusions.^{8,9} The other European/Australian study (protocol 020) had only 16 severe ARC or AIDS events partly because patients had to have a CD4 count $> 400/\mu\text{l}$ at entry and also the study was not analysed on a conventional intention to treat basis.⁷ An endpoint of clinical HIV disease was used which included oral candidiasis, leucoplakia and a CD4 endpoint of time to CD4 $< 350/\mu\text{l}$. Zidovudine was shown to delay progression time to this endpoint.

In Concorde the transient modest approximately 30 cell rise in CD4 counts and a persistent difference of around 30 cells between the immediate and deferred treatment groups over three years did not translate into an important clinical benefit. However, if a CD4 endpoint

Department of Sexually Transmitted Diseases, Division of Pathology, University College London Medical School and Camden and Islington Community Health Services NHS Trust
I V D Weller
I Williams

Address correspondence to: Professor I V D Weller, Academic Department of Genito-urinary Medicine, Mortimer Market Centre, Mortimer Market, off Copper Street, London WC1E 6AU.

Accepted for publication 15 December 1995

was used to assess efficacy, such as time to a CD4 count of $< 200/\mu\text{L}$, $< 350/\mu\text{L}$ or $< 50\%$ of baseline then a highly significant difference was seen between the two policies in favour of immediate therapy. The Concorde results therefore questioned the uncritical use of such modest changes in CD4 counts with monotherapy as a surrogate endpoint for mid to long term clinical efficacy, although the results supported their value as a prognostic marker for disease progression.¹⁰

Concorde also demonstrated a significant delay in ARC which largely consisted of oral candida and oral leucoplakia. However, such “soft” endpoints are difficult to assess objectively and to clarify and may be “CD4 driven”, that is, because physicians are not blinded to the CD4 count in trials they may be more likely to diagnose these conditions in patients with lower CD4 counts and therefore record them earlier in the treatment arms of trials with poor CD4 responses.

Furthermore, an analysis of Concorde using the same endpoints as ACTG 019 and only including those patients who had CD4 counts $< 500/\mu\text{L}$ at baseline demonstrated a trend in favour of immediate therapy (24 events in the immediate group, 37 events in the deferred group, $p = 0.09$). Concorde was not inconsistent with other studies, that is, it was consistent with a small early benefit that then disappeared.

One month before the full Concorde report appeared a retrospective quality of life analysis of the ACTG 019 trial was published using TWIST methodology (time without symptoms of disease or toxicity).¹¹ It showed that the increase in quality of life associated with a small delay in progression of disease at 18 months approximately equalled the decrease in quality of life associated with the earlier onset of severe side effects in the treatment group. Furthermore, in August of the same year further follow-up of the group of 1565 patients in ACTG 019 that entered with a CD4 count $< 500/\mu\text{L}$ followed for an average of 2.6 years showed that the delay in progression of disease diminished over time. Some patients (24.5%) were lost to follow-up before they reached a primary endpoint.¹²

There was much confusion following the Concorde results. Those who were certain that starting monotherapy with zidovudine early was the best strategy were less certain and/or spent some time trying to find fault with the study to explain a result that was in some ways difficult to digest. The results also indirectly raised questions about the longer term benefits of monotherapy even in symptomatic disease although the trial did not address that question.

Patients in Concorde and the three European/Australian trials (OPAL) were subsequently followed up by the MRC and ANRS HIV Clinical Trials Centres in London and Paris in collaboration with the Community HIV Research Network in Sydney.¹³ The median follow-up of this group of patients is over five years. In Concorde there was a significant excess of deaths in those who started

zidovudine immediately (Imm) compared to those in whom it was deferred (240 Imm deaths versus 199 in Def, log rank $p = 0.02$). In OPAL there was no significant difference in mortality between the groups (171 Imm, 188 Def, $p = 0.4$). These results emphasise the importance of the HIV Trialists Collaborative Group's plans to carry out a systematic overview of all trials in symptomless infection to better assess the effect of early antiretroviral therapy on mortality.

One of the many lessons to be learned from this series of events is that small early differences which emerge between groups in trials can be misleading. A more recent example of this was the Terry Bein Community Programs for Clinical Research on AIDS (CPCRA) study in which 467 patients who had previously received zidovudine with CD4 counts $< 300/\mu\text{L}$ were randomised to receive didanosine 500 mg daily or zalcitabine 2.25 mg daily.¹⁴ At two months a significant difference had emerged in CD4 counts between the two groups in favour of didanosine and at an early Data and Safety Monitoring Committee interim review there were 19 events in the ddI arm and 39 in the ddC arm (relative risk 2.08, $p = 0.009$).¹⁵ Ultimately, the study showed after an average follow-up of 16 months no overall difference between the groups in disease progression or mortality and if anything, after adjusting for baseline differences between the two groups, possibly a survival benefit in favour of zalcitabine.

Most studies have shown so far that CD4 endpoints assessed in trials at best only partially capture therapeutic effects.¹⁵ However, clinical trials have to show a reasonable degree of efficacy before change in any marker can be shown to capture therapeutic effect or failure. The Delta and ACTG 175 studies (see below) will provide very important data for such analyses, including virological markers. In the USA drugs have been provisionally licensed for monotherapy and combination therapy on promising early changes in CD4 counts and viraemia. It remains to be seen whether the same decision is made in Europe. In any debate about the use of surrogate versus clinical endpoints an assumption is made that our clinical endpoints are gold standards. They may not be. In most trials the primary outcome measure is a new or recurrent AIDS defining event or death. Since most trials have not had enough mortality endpoints the former influence efficacy results. However, there are 19 different events which are equally weighted and yet they vary for their risk of death.¹⁶ Events after the first are ignored. Effective treatments which may not have an immediate impact may be missed and such analyses do not account for endpoints which may be differentially affected by treatment. The problem with using time to a new or recurrent AIDS defining event was illustrated by Neaton *et al*¹⁶ by considering three patients in a trial, one who develops oesophageal candidiasis six months after randomisation but then remains stable until the end of the trial, one who dies after eight months and one who

develops oesophageal candidiasis after say nine months and later *Pneumocystis carinii* pneumonia and then at a later stage disseminated atypical mycobacterial infection. In an analysis of time to first event the first patient does worse and the third has the most favourable outcome!

Conditions such as oesophageal candidiasis, cryptosporidiosis and chronic herpes simplex virus infection carry a relative risk of death of around 1–1.7 (six month mortality 20–33%).¹⁶ Conditions such as *Pneumocystis carinii* pneumonia, wasting, cytomegalovirus disease and atypical mycobacterial infection have a relative risk of death of around 2.5 (six month mortality 33–44%). At the other extreme progressive multifocal leucoencephalopathy, lymphoma, visceral Kaposi's sarcoma and AIDS dementia complex carry a relative risk of death of 5–18 (a six month mortality of 50–85%). In other words those conditions associated with the greatest morbidity and risk of death are close to death. Neaton *et al* suggest that the primary endpoint in clinical trials should be survival and that all opportunistic events should be recorded, not just the first. Furthermore, these events should be weighted for severity to assess their influence on quality of life. A similar staging system which also takes account of CD4 counts was put forward by a group from London earlier this year.¹⁷

In August and September of 1995 the results of the Delta trials and ACTG 175 were announced.^{18,19} Delta 1 was a study in zidovudine naive patients and in Delta 2 patients had received at least three months treatment. In both trials patients were randomised to zidovudine monotherapy 600 mg daily or zidovudine plus didanosine (400 mg daily) or zidovudine plus zalcitabine (2.25 mg daily). In Delta 1 2191 patients were randomised. The mean CD4 count at entry was 213/ μ l and the median follow-up time was 26 months. Combination therapy improved survival over monotherapy. Of 703 patients in the zidovudine monotherapy arm 16.5% died compared with 9.6% of 720 and 11.6% of 708 in the didanosine and zalcitabine combination groups respectively (global log rank $p = 0.0003$). The two combinations did not differ significantly. Combination therapy also significantly delayed progression to AIDS or death. Of 623 patients 28.4% in the zidovudine monotherapy arm developed AIDS or died compared with 17.6% of 630 and 23.3% of 615 in the didanosine and zalcitabine combination groups respectively (global log rank $p < 0.0001$). There was a suggestion that the didanosine combination group fared better than the zalcitabine group. In Delta 2 there were no significant differences detected between the monotherapy and combination groups in terms of survival or disease progression. However, a benefit from combination therapy in this group was not excluded. Combining the results of both Delta 1 and Delta 2 yields a reduction in mortality of about 25% in favour of combination therapy ($p = 0.001$).

ACTG 175 differed from Delta in a num-

ber of ways. The trial included both zidovudine naive and exposed patients. It included a second monotherapy arm, namely, didanosine alone. The baseline CD4 count of the 2467 participants was higher at entry (mean 352) so there were fewer clinical events in a longer median follow-up time (36 months) and the primary endpoint included time to a 50% decline in CD4 count as well as to new or recurrent AIDS event and death. In a planned sub-group analysis in zidovudine naive patients (43% of the population) both combination arms (zidovudine with didanosine and zidovudine with zalcitabine) and didanosine monotherapy were each superior to zidovudine alone with respect to the combined primary endpoint (progression rates of 14%, 10%, 17% and 23% respectively). For the pure clinical endpoint of AIDS or death zidovudine with zalcitabine was significantly superior to zidovudine monotherapy. In zidovudine experienced patients the two combination regimens and the didanosine monotherapy "the switch regimen" were superior to the zidovudine monotherapy arm with respect to progression to the primary endpoint and zidovudine/didanosine and didanosine switch both conferred a clinical benefit when only the clinical endpoints were considered. The clinical event rate in the zidovudine/zalcitabine arm was comparable to the zidovudine monotherapy arm. Caution is needed before assuming that didanosine is superior to zidovudine as monotherapy in naive patients. There was a "blunted" CD4 response in this group with zidovudine monotherapy which suggests that a proportion of patients may not have been truly zidovudine naive. Nevertheless, the overall results of ACTG 175 are largely driven by the zidovudine experienced patients. Furthermore, more information on the value of adding a second drug in zidovudine exposed patients will be obtained with the imminent results of a similar trial to Delta carried out by the CPCRA, protocol 007 (the NUCOMBO trial).

We are now on an "up" again. The results of these studies clearly show that two drugs are better than one. There are a number of phase II and III trials using two, three and even four drugs in combination in progress or being planned. These trials include new nucleosides, non-nucleoside reverse transcriptase inhibitors and the protease inhibitors. We all hope that even greater efficacy and safety will be demonstrated. However, for the clinician with the current drugs available three important questions remain. These are: when to start therapy, when to change (switch/combine) and when to stop. The latter may be viewed as too nihilistic at a time when our hopes now have been raised but will remain a very important question.

The results of Delta and 175 do not tell us when to start therapy. Delta 1 was a late intervention. The mean CD4 count was 213/ μ l and 12% of the patients had AIDS. There was no evidence that benefit was any different in those that entered the trial symptomless compared to those with AIDS. Only a trial of immediate

versus deferred combination therapy will address this question. The simple answer to the question of When to start, is start when you did before you saw the results of these trials, but use two drugs rather than one. It is clear that adding another drug or switching to another drug may produce clinical benefits in terms of time to the next AIDS defining event but the question is when should one change therapy. There is no clear answer. We hope that viral markers such as viraemia, genotypic and phenotypic resistance measures will in the future help us determine this. At the moment a pragmatic approach would be to switch when a patient becomes intolerant to a drug and to switch or add when a patient is deteriorating clinically. Physicians will define the latter in different ways.

Those who favour early intervention tend to justify it on biological plausibility rather than evidenced based medicine. From observations on the initial rapid decrease in viraemia seen with antiviral agents the half life of virus has been independently estimated as being around two days, that is, around 50% of the viral population turns over within 48 hours. There is a daily production/clearance of around a billion virions and a similar number of CD4 cells are destroyed daily. Furthermore, the reverse transcriptase is error prone. It does not have a function to correct mistakes. It makes errors on average 1 per 1700 incorporated nucleotides. Single point mutations therefore occur in the reverse transcriptase around 10^4 times a day. The reverse transcriptase has 500 amino acids with 20 possibilities at each residue. Therefore, within a few years although many viruses will die out because of lethal mutations, a complete repertoire of HIV mutants exists only to be selected by monotherapy and also perhaps by certain combinations to become the dominant virus. Newly infected patients therefore have fewer variants and early therapy must make sense.^{20 21 22} The recent placebo-controlled study of zidovudine in 77 patients with acute HIV infection concluded that early intervention at this stage may increase CD4 count and delay progression of disease.²³ However, only eight patients developed clinical endpoints consisting of oral candida, herpes zoster and oral hairy leucoplakia.

The late interventionists share the hopes of the early starters but are waiting for more evidence around the risk:benefit ratio. The battle cry of "time to hit HIV, early and hard" is a virological philosophy which we all share but would not want to put into practice without better knowledge of the long term risks of the current drugs that we have available particularly in combination.²⁴

- 1 Fischl MA, Richman DD, Grieco MH, *et al*, and the AZT Collaborative Working Group. The efficacy of azidothymidine (AZT) in the treatment of participants with AIDS and AIDS-related complex: a double-blind,

- placebo-controlled trial. *N Engl J Med* 1987;317:185–91.
- 2 Volberding PA, Lagakos SW, Koch MA, *et al*, and the AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases. Zidovudine in asymptomatic human immunodeficiency virus infection. *N Engl J Med* 1990;322:941–9.
- 3 Fischl MA, Richman DD, Hansen N, *et al*, and the AIDS Clinical Trials Group. The safety and efficacy of zidovudine (AZT) in the treatment of subjects with mildly symptomatic human immunodeficiency virus type 1 (HIV) infection. *Ann Intern Med* 1990;112:727–37.
- 4 Kahn JO, Lagakos SW, Richman DD, *et al*. A controlled trial comparing continued zidovudine with didanosine in human immunodeficiency virus infection. *N Engl J Med* 1992;327:581–7.
- 5 Hamilton JD, Hartigan PM, Simberloff MS, *et al*, and the Veterans Affairs Cooperative Study Group. A controlled trial of early versus late treatment with zidovudine in symptomatic human immunodeficiency virus infection. *N Engl J Med* 1992;326:437–43.
- 6 Aboulker J-P, Swart AM. Preliminary analysis of the Concorde trial. *Lancet* 1993;341:889–90.
- 7 Cooper DA, Gatell JM, Kroon S, *et al*, and the European-Australian Collaborative Group. Zidovudine in persons with asymptomatic HIV infection and CD4 + cell counts greater than 400 per cubic millimetre. *N Engl J Med* 1993;329:297–303.
- 8 Mulder JW, Cooper DA, Mathiesen L, *et al*, and the European-Australian Collaborative Group. Zidovudine twice daily in asymptomatic subjects with HIV infection and a high risk of progression to AIDS: a randomised, double-blind, placebo-controlled study. *AIDS* 1994;8:313–21.
- 9 Mannucci PM, Gringeri A, Savidge G, *et al*, for the European-Australian Haemophilia Collaborative Study Group. Randomised double-blind, placebo-controlled trial of twice-daily zidovudine in symptomatic haemophiliacs infected with the human immunodeficiency virus type 1. *Br J Haematol* 1994;86:174–9.
- 10 Concorde Coordinating Committee. Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet* 1994;343:871–80.
- 11 Lenderking WR, Gelber RD, Cotton DJ, *et al*, and the AIDS Clinical Trials Group. Evaluation of the quality of life associated with zidovudine treatment in asymptomatic human immunodeficiency virus infection. *N Engl J Med* 1994;330:738–43.
- 12 Volberding PA, Lagakos SW, Grimes JM, *et al*. The duration of zidovudine benefit in persons with asymptomatic HIV infection. Prolonged evaluation of protocol 019 of the AIDS Clinical Trials Group. *JAMA* 1994;272:437–42.
- 13 Darbyshire J on behalf of the Joint Concorde/Opal Coordinating Committee—"late breaker" abstract. Fifth European Conference on Clinical Aspects and Treatment of HIV Infection. Sept 26–29 1995, Copenhagen, Denmark.
- 14 Abrams DI, Goldman AI, Launer C, *et al*. A comparative trial of didanosine or zalcitabine after treatment with zidovudine in patients with human immunodeficiency virus infection. *N Engl J Med* 1994;330:657–62.
- 15 Fleming TR. Surrogate markers in AIDS and cancer trials. *Statistics in Medicine* 1994;13:1423–35.
- 16 Neaton JD, Wentworth DN, Rhame F, Hogan C, Abrams DI, Deyton L for the Terry Bein Community Programs for Clinical research on AIDS (CPCRA). Methods of studying interventions: considerations in choice of a clinical endpoint for AIDS clinical trials. *Statistics in Medicine* 1994;13:2107–25.
- 17 Mocroft AJ, Johnson MA, Sabin CA, *et al*. Staging system for clinical AIDS patients. *Lancet* 1995;346:12–7.
- 18 Yeni P on behalf of the International Coordinating Committee. Preliminary results of the European-Australian Delta trial based on data up to 31st May 1995—"late breaker" abstract. Fifth European Conference on Clinical Aspects and Treatment of HIV Infection. Sept 26–29 1995, Copenhagen, Denmark.
- 19 Hammer S, Katzenstein D, Hughes M, Gundacker H, Hirsch M, Merigan T of the ACTG 175 study team—"late breaker" abstract. Fifth European Conference on Clinical Aspects and Treatment of HIV Infection. Sept 26–29 1995, Copenhagen, Denmark.
- 20 Wei Y, Ghosh SK, Taylor ME, *et al*. Viral dynamics in human immunodeficiency virus type 1 infection. *Nature* 1995;373:117–22.
- 21 Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature* 1995;373:123–6.
- 22 Coffin JM. HIV population dynamics in vivo: implications for genetic variation, pathogenesis and therapy. *Science* 1995;267:483–9.
- 23 Kinloch-de Loës S, Hirschel BJ, Hoen B, *et al*. A controlled trial of zidovudine in primary human immunodeficiency virus infection. *N Engl J Med* 1995;333:408–13.
- 24 Ho DD. Time to hit HIV, early and hard. *N Engl J Med* 1995;333:450–1.